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Division of Research Services

Annual Report

Fiscal Year 1984

National
Institutes
of Health

The Division of Research Services

The many specialized functions of the Division are designed to support all of the 18 Bureaus, Institutes, and Divisions (BIDs) which constitute the National Institutes of Health. The primary program emphasis, however, is directed at serving the 8,000 staff members of the intramural program, including more than 2,600 doctoral level scientists who conduct research in NIH laboratories.

Organizationally, the Division is structured to provide products and services in support of the sequential steps in every biomedical research project: planning, making available models and substrates, manipulating and measuring research materials, and recording and communicating research results.

- The Library Branch possesses or has access to virtually all published biomedical knowledge to assist the investigator in planning and designing his/her project.
- The Veterinary Resources Branch provides the animal models, organic materials, and proper facilities for their use.
- The Biomedical Engineering and Instrumentation Branch collaborates with the investigator in devising the means whereby research materials may be manipulated and results measured, often with highly sophisticated electronic equipment.
- Finally, the skills of the Medical Arts and Photography Branch are available to all investigators to enable them to record the results of their research and communicate them to the scientific community.

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Division of Research Services

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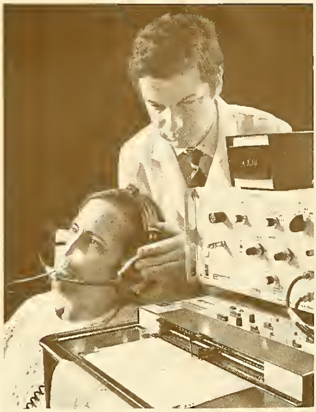

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A Letter From the Director

Joe R. Held, D.V.M., Director
Division of Research Services
National Institutes of Health

I am writing this introduction to the DRS Annual Report for Fiscal Year 1984 shortly before leaving my post as Division Director for new duties as Director of the Pan American Zoonoses Center in Buenos Aires, Argentina. This will be a return to a Pan American Health Organization program where I served from 1967 to 1969 on a detail from the U.S. Public Health Service.

In reflecting on the activities of the nearly 500 DRS staff members during the 12 years I have been Division Director, I have been impressed especially by the steady increase in two different kinds of teamwork: collaborative research involving DRS staff with intramural investigators of the NIH Institutes, and the cooperation between our four Branches and the DRS Office of the Director to provide high quality services and products to the intramural program as effectively and economically as possible.

Collaborative research involving biomedical engineering received a major boost when Dr. Murray Eden became the Chief of the Biomedical Engineering and Instrumentation Branch in 1976, and it has blossomed ever since. A notable example is the many applications of laser technology that BEIB engineers and physical scientists are currently developing with staff of six separate Institutes as well as the Division of Computer Research and Technology and the Division of Blood and Blood Products in the Food and Drug Administration. These laser projects are featured in the BEIB section of this report.

In the Veterinary Resources Branch, Dr. Robert A. Whitney, Jr., has motivated his staff so that the primary concern of VRB is responsiveness to the needs of NIH intramural investigators. This includes much collaborative research, especially projects involving large animals in VRB's Veterinary Medicine and Surgery Section. Since 1983 Dr. Whitney and his staff have also been providing holding of small laboratory animals on experiment, in a facility renovated so that Institute scientists can function in an ideal location with VRB personnel performing many of the necessary manipulations. This year the new holding facility was operating at full capacity.

The many articles co-authored by Institute investigators and staff members of BEIB and VRB represent only a part of their collaboration. And the contributions made by staff members of the NIH Library and the Medical Arts and Photography Branch are such that their work is also an integral part of NIH intramural research. The collaboration of personnel from these Branches is nearly always required in planning research and in presenting and publishing results. I am grateful to Mrs. Carolyn Brown, Chief of the Library Branch, and Mr. Ronald Winterrowd, Chief of MAPB, for their maintenance of high standards in that effort.

All four Branches have shown the same spirit of collaboration in working with the Office of the Director, DRS, as they have shown in meeting scientists' research needs. We have been striving together to keep the costs of our services and products as low as is consistent with excellence. Those products and services that can be obtained more economically by contract rather than in-house have been identified; about one-third of the DRS budget is now expended for items purchased by contract. In-house operations involving a discrete service or product that can be measured for rational billing of an individual user are handled on the Service and Supply Fund, and the user is charged. The DRS activities funded by the Management Fund, without such cost recovery, are only those for which no discrete service or product can be identified.

Over the years, initiatives to improve our operations have come both from the Branches and from the staff of our Office of the Director. Our Executive Officer, John Smart, has heightened this collaboration, bringing to his post the perspectives of an intramural administrative officer, always conscious of the needs of intramural researchers and administrators.

In summary, DRS is working very well, and can be expected to continue to do so. I am grateful for the opportunity I have had to serve in this capacity for the past 12 years, and to have been part of such an enthusiastic group dedicated to furthering the programs of NIH.

Division of Research Services FY 84 Budget (in thousands of dollars)

Branch	Management	Service & Supply	Total
Veterinary Resources	$4,757	$8,194	$12,951
Biomedical Engineering & Instrumentation	2,926	6,250	9,176
Library	3,375		3,375
Medical Arts & Photography	662	5,621	6,283
Total	$11,720	$20,065	$31,785

Publications

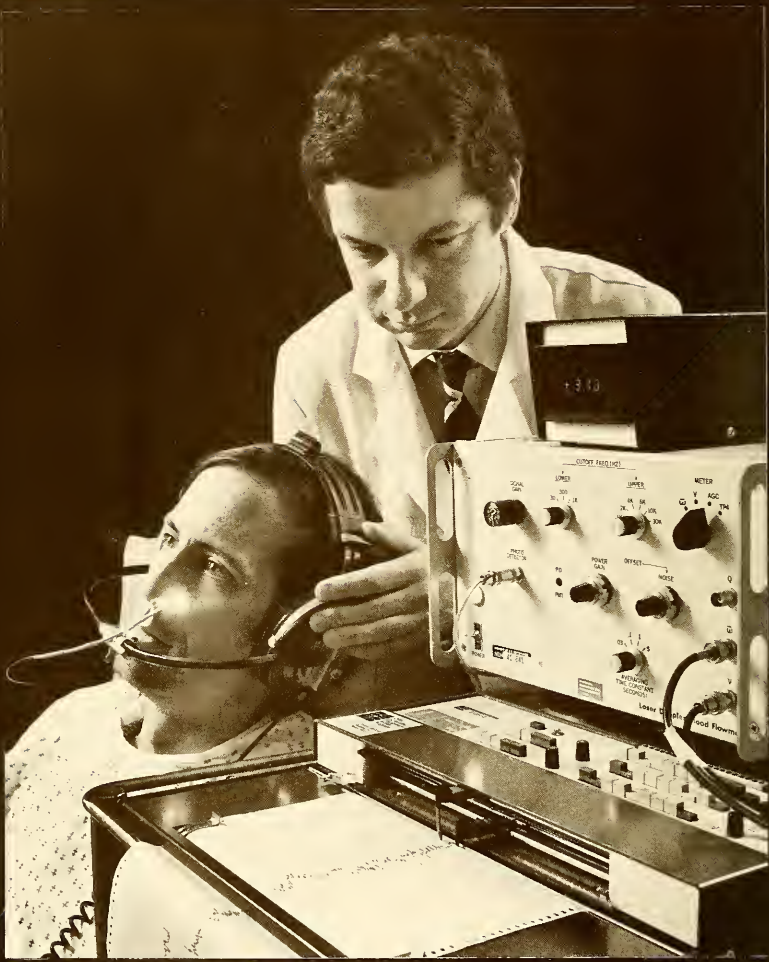
Held, J.R.: Cats and rabies. *Carnation Research Digest* 20 (2):1-5, 15, 1983

Held, J.R.: Defending animal use in biomedical research (Guest editorial). *Pharmaceutical Technology* 8 (10):16-17, 1984.

Held, J.R.: Quality animals for biomedical research: lessons from the past, opportunities for the future. In Melby, E.C., Jr., and Balk, M.W. (Eds.): *The Important of Laboratory Animal Genetics, Health and the Environment in Biomedical Research.* New York: Academic Press, Inc., 1983, pp. 259-267.

Held, J.R., Doherty, J., and King, N.B.: Societal benefits derived from animal research. *Journal of the American Veterinary Medical Association* 185 (3):268-269, 1984.

Held, J.R., and Gay, W.I.: Primate research resources in the Soviet Union. *Journal of Medical Primatology* 12:77-88, 1983.



The Laser Doppler Blood Flow Monitor, developed by the Biomedical Engineering and Instrumentation Branch and the Laboratory of Technical Development, NHLBI, measures the velocity and flow rates of red blood cells within blood vessels. Its ability to distinguish the entire range of physiological changes in blood flow is unique.

Biomedical Engineering and Instrumentation Branch

Murray Eden, Ph.D., Chief

Until recently the only way a blood bank could assess the quality of the platelets in a storage bag has been to break the bag's sterile seal and examine its contents. The Biomedical Engineering and Instrumentation Branch (BEIB), NIH's focus for expertise in engineering and related sciences, has recently completed three years of development on an automated device that leaves the sterile seal on the storage bag intact, while automatically measuring the quantity and viability of the platelets inside. This noninvasive procedure offers the potential to improve the quality of the over two million units of concentrated platelets that hospitals transfuse annually.

A group within the Division of Blood and Blood Products in the Food and Drug Administrtion (FDA) noticed that a suspension of "good" platelets looked different from a bad unit. They approached BEIB, asking "How can we measure this effect?"

The team within BEIB that solved the problem consists of an optical biophysicist, an electro-optical physicist, electrical engineers, and a mechanical engineer. The solution was based upon the varying degree to which cells of various shapes scatter laser light as their orientation to the light changes. For asymmetric cells, such as normal platelets, the amount of scatter depends strongly on orientation; for irregular or spherical cells, such as aged platelets, it does not.

BEIB's device shines a laser beam through the clear plastic of the sealed storage bag. It then gently squeezes the bag, causing the suspended platelets inside the flow. Normal platelets are discoid and align their axes with the flow. Platelets that are more nearly spherical do not show this effect. Differences in the degree of scatter during flow and rest allow the device to compute the number of platelets and the fraction that are normal. This noninvasive assessment by light, based upon low-angle multiple scattering theory, is at least as accurate as the time-consuming, invasive techniques of precise dilution, Coulter counting, and *in vitro* functional assessment.

Members of the team have also applied the special properties of laser light (temporal coherence and a highly collimated beam) in the development of another noninvasive diagnostic instrument: the Laser Doppler Blood Flow Monitor. This device, reminiscent of traffic radar, uses a Doppler-shift principle to measure the velocity and flow rates of red blood cells as they course through microvessels. Light is an ideal physical probe of the red blood cells, because it interacts strongly with them. The laser technique can easily measure velocities as small as .4 mm/sec (about one inch per minute). By simultaneously averaging the flow in more than a hundred microvessels at the surface of an organ, the technique provides a continuous evaluation of flow. The clinical version of the instrument, developed collaboratively by BEIB and the Laboratory of Technical Development, National Heart, Lung, and Blood Institute (NHLBI), uses state-of-the-art optical fibers to detect the light's interactions in patients. A specially designed analog processor gives continuous readings of microcirculatory blood flow by instantaneously computing mean Doppler shift, as well as the fraction of the signal that is shifted. This instrument is unique in its ability to resolve continuously the entire range of physiological changes in blood flow. BEIB and the Physical Sciences Laboratory of the Division of Computer Research and Technology (DCRT) have collaboratively developed the theory needed to interpret clinical measurements with the technique. Its clinical usefulness is being evaluated in a series of protocols by five NIH Institutes: the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), National Institute of Allergy and Infectious Diseases (NIAID), National Eye Institute (NEI), National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK), and NHLBI.

Neurologists in NINCDS and BEIB have used the device to demonstrate the abnormal microcirculatory responses that ischemia causes in the muscles of patients with certain neuromuscular diseases. Additionally, the study has established techniques for routine use for the instrument during surgery.

An extensive collaborative study by the Laboratory of Clinical Investigation, NIAID, and BEIB has demonstrated the device's usefulness for monitoring the responses of nasal blood flow to vasoactive drugs; this capacity is the basis for further studies of allergic responses.

The NEI and BEI have begun a study of microvascular flow in the skin of diabetics, perhaps eventually allowing assessment of microvascular changes associated with long-term disease and various therapeutic regimes.

The Hypertension-Endocrine Branch, NHLBI, and BEIB have applied the device to the study of microcirculatory dynamics in hypertensive patients and to quantification of the effects of vasoactive medications. The studies are intended to assess the microcirculation's role in the etiology of essential hypertension.

In collaboration with clinicians in NIADDK, NHLBI, and the Clinical Center (CC), BEIB has performed a series of experiments that characterize the distinctive microvascular responses found in patients with sickle cell disease. These responses to abnormal red cells appear to be connected intimately to the patient's ability to maintain blood flow through tissues, despite the tendancy of the poorly deformable red blood cells to obstruct microvessels. Preliminary results suggest that these microvascular responses may be of critical importance in understanding the variable course of this genetic disease.

The Branch has also been busy fulfilling its commitment to provide the NIH research community with a broad range of scientific and engineering expertise. For example, BEIB has collaborated in more than 200 projects to produce advanced instrumentation, models, methods, and techniques dedicated to the acquisition by NIH's scientists of biomedical information previously unavailable.

The staff of approximately 45 professional physical scientists and engineers and 80 technical support personnel responded to over 3,000 requests for the fabrication and modification of laboratory devices and made another 9000 repairs and minor changes of scientific equipment.

In addition, BEIB is cooperating with the government of Egypt and the governments of several Caribbean nations to increase their capability to maintain hospital and scientific equipment. Funding for these projects is provided by the U.S. Agency for International Development (AID). In each of these projects BEIB and AID are attempting to train new personnel and modify operations to meet changing needs after BEIB's participation in the program ends.

BEIB's professional staff functions within four sections and the Office of the Chief. Here is a brief description of their activities for FY 1984.

Applied Clinical Engineering Section (ACES)
This section, located in the Clinical Center, offers expertise in a variety of engineering problems arising in biomedical research. For example, the group is refining flow cytometry systems used clinically and experimentally in the diagnosis and treatment of various diseases. The contributions of the ACES in these endeavors range from fine tuning of the optical and electronic components of the flow cytometer's instrumentation to development of novel mathematical approaches for display and interpretation of data acquired from clinical cell populations.

Last year the Laboratory of Parasitic Diseases, NIAID, incorporated a new flow cell, which ACES designed, into a flow cytometer used in studies of protozoan parasites. This new cell combined improved optical coupling techniques with simplified fluidic components to produce greatly improved performance.

The CC's Clinical Pathology Department has begun to use algorithms that the ACES developed in the interpretation of cytometric data. These algorithms smooth and clarify data, permitting clinician to make more conclusive diagnoses.

The efforts of the ACES in the past year have brought about significant refinements in the micro-calorimeter developed in collaboration with the Laboratory of Technical Development, NHLBI. To satisfy clinical requirements, ACES increased the cell volume to one milliliter. This change initially produced an erratic mixing artifact, averaging an intolerable 900 microjoules. ACES determined the source of this artifact to be a temperature gradient of merely .004 °C within the microcalorimeter's chamber. By carefully shunting currents through the temperature-controlling heating pads in the calorimeter, the team reduced the gradient to less than .0005 °C, concomitantly lowering the mixing artifact to approximately 100 microjoules. Additionally, ACES has undertaken the design of a microprocessor-based, differential scanning calorimeter that will incorporate the high technology used in the present microcalorimeter to produce a scanning calorimeter that will incorporate the high technology used in the present microcalorimeter to produce a scanning calorimeter with sensitivity at least ten times greater that that of available instruments.

The ACES has also collaborated with the Diagnostic Radiology Department and the Rehabilitation Medicine Department of the CC and the Acoustics Laboratory, NINCDS, to advance the field of speech pathology. These groups now use a prototype, which the ACES designed, for simultaneous tracking of the movements of the upper and lower lips during speech. This aids the diagnosis of certain speech disorders and helps to evaluate the efficacy of therapeutic interventions. Currently, the collaborators are testing unique ultrasonic transducer holders, designed by the ACES and BEIB's Mechanical Instrumentation Fabrication Shop, to obtain images of the tongue during speech. This holder must ensure proper acoustical coupling of the ultrasonic transducer under the chin, while introducing minimal interference to jaw movement.

In conjunction with the Surgery Branch, NCI, the ACES is investigating the pathophysiology of the general debilitation commonly accompanying sarcoma. This metatastic disease lends itself to metabolic studies, because the patient's alimentary processes are rarely impaired. The ACES developed instrumentation that permits the indirect quantification of certain metabolic indicators, such as stable isotopes in the form of 13C-glucose, 15N-glycine, and 13C-leucine. So far this study has demonstrated a marked increase in energy expenditure in patients with metastatic disease. The next phase of this research is intended to determine if glucose oxidation, whole-body protein turnover, and potassium-40 levels are abnormal preoperatively in patients with sarcoma.

Other instruments developed by the ACES this year included a temperature-controlled hypobaric chamber for X-ray diffraction specimens; a radiolucent window and solid-state heat pump to improve X-ray diffraction images dramatically; and a modified incubator for uniformly irradiating cell cultures under controlled condition as temperature, humidity, and carbon dioxide concentration.

The ACES continues to provide support to the safety program in the Clinical Center/ACRF. This program provides for the biannual safety inspection of all patient-related electrical instruments. The ACES maintains the information collected in a large computerized data base, readily accessible for analysis or verification.

Chemical Engineering Section (ChES)

The Chemical Engineering Section has continued its activities in biomedical instrumentation, fluid mechanics, biomaterials, and the mathematical analysis of drug distributions in the body. This year the group directed considerable activity in each of these disciplines toward a common program area: regional drug administration for the treatment of tumors.

In collaboration with NINCDS the group developed a general pharmacokinetic theory concerning arterial infusions of drugs, as well as subsequent removal of the drugs from venous blood by an extracorporeal device. Intra-arterial regional chemotherapy of this sort offers an alternative to systemic treatments, when the tumor is well localized. This approach is less fraught with side effects, because high drug concentrations at the tumor site are possible without systemic toxicity.

This pharmacokinetic advantage is achievable only if a sufficient fraction of the venous blood passes through the extracorporeal device and if the device is sufficiently efficient. In collaboration with the CC and NINCDS, BEIB tested the theory. using intracarotid infusions of the chemotherapeutic agent BCNU in anesthetized monkeys, during removal of drug by an organic adsorbent in a hemoperfusion column. The procedure reduced systemic exposure by 46 to 84 percent, compared to intravenous infusions of the same dose. Because success of the treatment depends on a knowledge of the fraction of venous drainage that can be shunted into the extracorporeal device, BEIB concurrently developed a dye-dilution technique, using indocyanine green, to estimate this parameter. After the mathematical analysis and testing in animals, BEIB collaborated with the CC and NINCDS to apply the intra-arterial perfusion procedure to treatment of malignant gliomas in four patients.

A related project involved the development of a specialized catheter to provide localized arterial infusions. The site of intended infusion is frequently inaccessible with conventional catheters, and surgical intervention is often too risk-prone for the patient. The Section has designed a double-lumen arterial catheter that clinicians can steer and propel by controlling jets of fluid that flow through small holes on either side of the catheter's tip. A specially designed manifold switches from saline, the propulsion fluid, to the chosen drug, once the tip of the catheter is in place. BEIB coats the catheter's outer surface with bonded hydrogel to reduce drag on the arterial walls. In tests in anesthetized Rhesus monkeys the jet catheter proved capable of negotiating arteries impassable by conventional catheters.

The Section has also studied the fluid mechanics of the jet flows issuing from various catheter tip designs. This is an area of concern, because the efficacy of intra-arterial infusions in treating tumors appears to depend upon adequate mixing of blood and drug—a factor in turn dependent upon catheter design. Engineers in the Section have used several types of flow models to discover the factors that govern mixing.

Another of the Section's major endeavors was refinement of a lumped-compartmental model for administration of the chemotherapeutic drug cis-platin. This projects relates to the regional perfusion studies described above, because cis-platin is a candidate drug for use in intra-arterial treatment of malignant gliomas. The group developed a more detailed description of cis-platin's binding to various macromolecules, as well as an improved distributed model for cis-platin's transport in peritoneum and brain. In conjunction with BEIB's Electron Beam Imaging and Microspectroscopy Group, the Section studied the penetration of cis-platin into peritoneal and sub-peritoneal tissue in Sprague-Dawley rats using an electron probe to perform elemental microanalysis. The Section then repeated these experimental-to-theoretical comparisions for concentration profiles of cis-platin in the cortex and cerebellum of rats.

In addition, the Section continued to advance its work in such areas as fiberoptic oxygen probes, membrane-based *in vivo* sampling systems, biomaterials, and fluid mechanical effects of blood on arterial endothelial cells.

Electrical and Electronic Engineering Section (EEES)

The Electrical and Electronic Engineering Section continued its program of applying the power of modern electronic technology to the needs of biomedical research. The opening paragraphs of this report described in some detail two of the Section's major projects involving electro-optics. Another potentially major project in this area is a new collaboration with the Surgery and Cardiology Branches of the NHLBI, NASA Goddard, and the Naval Research Laboratory (NRL). This will involve the use of laser energy to remove deposits of plaque in coronary arteries in the treatment of coronary heart disease. First the Section intends to connect a coherent-bundle fiberoptic angioscope to a video system to allow monitoring and recording of conditions in the artery before and after laser treatment. This will facilitate evaluations of the ability of various laser sources to selectively ablate plaque with minimal arterial damage. Carbon dioxide and argon ion lasers have been used for laser surgery; they function by vaporizing matter. Another possibility, which the Section will explore, is photochemical decomposition of the deposits by ultraviolet radiation from an excimer laser. NASA Goddard and the NRL will provide laser sources not available at NIH. The success of the laser ablation will be evaluated by studying the thermal profile in animal and cadaver arteries, following the laser pulse, as well as by histopathological studies. BEIB will use miniature thermistors and an infrared video system to measure the requisite thermal profiles. The Section will then develop the system for delivering laser energy to the desired sites in coronary arteries, utilizing either waveguides or fiber-optic light guides, depending upon the type of laser selected.

In another electro-optic project, the Section supported a study of cell fusion and aggregation undertaken by researchers in NINCDS. BEIB designed custom optics for a stop-flow apparatus, as well as an interface for a PDP 11/34 computer used in data acquisition and processing.

With the effort on the Neuro-PET (Neuro Positron Emission Tomography) scanner tapering off sharply, as usage becomes routine, the Section has redeployed those resources to another major project: magnetoencephalography (MEG). In collaboration with the Medical Neurology Branch, NINCDS, and the Naval Research Laboratory, the Section has begun efforts to develop a system for localizing epileptic foci in three dimensions. Long experience has demonstrated that surface EEG measurements are insufficient for this, largely because of the insulating properties of the skull and the difficulties of producing adequate mathematical models. MEG, although a difficult technique, is free of this problem and is capable of localizing the site of auditory-evoked responses.

EEG-based analyses of evoked potentials rely heavily on time averaging, which is of little or no use with epileptic discharges. To compensate for this difficulty, the Section hopes to use concurrent EEG and MEG data, and it is exploring signal processing techniques that can extract desirable information from considerable background noise. In addition, procurement of a seven channel array is in progress; this device will further reduce the need for time averaging.

Two new projects in collaboration with the Laboratory of Technical Development, NHLBI, are of particular interest. The first is a study of fluoroimmunoassay techniques as an alternative to radioactive and enzyme immunoassays. Fluorescence techniques are simple, safe, and convenient, but their sensitivity has been low because of interference from the normal background fluorescence of almost all organic materials. Recently, rare-earth-chelate fluorescent probes have been developed with decay-time constants an order of magnitude greater than background time constants, affording in principle an opportunity to increase greatly the sensitivity of the method. Overload recovery of the detector is a problem, however, and the solutions developed for high speed, high fluorescence work do not apperar to be satisfactory for the low speed, ultralow-level requirements of this application. EEES is conducting a broadly based study to develop the detector and overload circuitry. The Center for Disease Control, which is interested in the method as a tool for research into Acquired Immunological Defficiency Syndrome (AIDS), is providing support and collaborating on biochemical problems that appear at extremely low chemical concentrations.

The other project, in which Corning Glass Works is collaborating, is intended to incorporate a miniature preamplifier into an otherwise ordinary specific-ion electrode. It is intended that the resulting device can be used directly with computerized digital data acquisition systems, rather than with electrometers, allowing the computer to handle calibration, temperature compensation, and the like. This approach provides some of the benefits that were generally expected five years ago from a different technology—ion selective field-effect transistor (ISFET) electrodes—but do not appear realizable in that way.

This past year, the ever increasing role of computers in biomedical research was reflected in the incorporation of a microcomputer into the large bus-oriented instrumentation system that BEIB originally developed for a fermentation system in NIADDK. The Section also interconnected a custom flow cytometry cell (developed by BEIB's ACES) to a computer, and developed requisite software. Similarly, BEIB incorporated a computer into an elaborate environmental monitoring and control system for animal facilities of the DRS Veterinary Resources Branch (Building 14) to meet the specific needs of an NIAID research program.

As always, the Section continued substantial effort on older projects, a variety of consultations, and smaller new projects in such areas as video systems, microprocessor-based instruments, data acquisition systems, and controllers.

Several new developments promise to enhance the capabilities of the Section. The EEES is beginning to exploit the capabilities of a new digital oscilloscope. This instrument has many desirable features, such as storage, pre-trigger record, and hard copy output, as well as many digital processing functions, such as spectral analysis, auto- and cross-correlation, averaging, multiplication of traces, convolution, and integration—all available at the touch of a button. Because the instrument is portable, engineers in the Section can easily take it to labs where they can use it to experiment easily with a variety of signal processing approaches; this is expected to be most helpful during the definition phase of a project. EEES is also acquiring a computer-based digital data acquisition system, and in the coming year will install a work station for computer-aided design and engineering. Initial capabilities of the system will include electronic drafting, two-dimensional mechanical drafting, logic simulation, and automated generation of wiring and parts lists.

Mechanical Engineering System (MES)

The Mechanical Engineering Section conducted a wide diversity of collaborative efforts with members of NIH's intramural research program, involving analytical and experimental studies and the development of specialized instrumentation. A multi-year effort in collaboration with the Radiation Oncology Branch, NCI, is making substantial progress in the development of equipment and protocols for regional microwave hyperthermia, used as an adjunctive treatment for cancer. The goal is to gain better understanding of electromagnetic and thermal processes in tissue and to improve the efficacy of systems under development. In order to determine patterns of energy deposition in tissue, the group has used a large-scale computerized "block model" of man, as well as various types of electric field and temperature probes in conjunction with various microwave applicators.

The Section has shown that some hyperthermia protocols, developed elsewhere, can cause undesirable heating outside of an intended region in a patient's body. In addition, the Section has developed new types of phantom materials to simulate the microwave properties of tissue, and it is developing a new biomass and heat transfer model that accurately incorporates the effects of blood flow. The MES anticipates that the integration of these experimental and analytical efforts will culminate in the development of a clinical system, using computer-controlled protocols, within the next two years.

The Section continues its innovations in biomechanics. It has coupled a theory of the propagation of pressure pulses in arteries with a mathematical model of the left ventrical, allowing studies of the interaction between the two systems. In work with the Hypertension-Endocrine Branch, NHLBI, analysis of clinical data on the pulse wave in the brachial artery has resulted in improved understanding of the mechanics of vasoactive responses in both normal and hypertensive patients. A mathematical model of arteriolar contraction was developed to study the mechanism of reduction in lumenal area, taking into account certain properties of endothelial cells. Moreover, a new study aimed at assessing the role of vascular tortuosity in vascular resistance was undertaken, using both theoretical and physical models. In the area of cochlear processing, the Section collaborated with the Mathematical Research Branch, NIADDK, to complete a theoretical model for the ear incorporating basilar membrane motion, couplings between fluid and cilia, and hair cell transduction.

Last year the Section developed an improved version of the toposcopic catheter—a device that moves through blood vessels with minimal friction. The new implementation is easier to use and can deliver high flow rates, such as those required in a clinical protocol under way with the Diagnostic Radiology Department, CC. In a collaboration with the Department of Gastroenterology, Naval Medical Command, Bethesda, Maryland, the Section has adapted the catheter so that it can fit through a duodenoscope used for endoscopic retrograde cholangiopancreatography (ERCP) and other clinical procedures of the gastrointestinal tract. The catheter was honored with a 1984 I-R 100 Award, presented by *Research & Development* magazine. The Section is also developing the capability of extruding miniature tubing with various cross sections.

Collaboration with the Laboratory of Biophysics, NINCDS, to develop a miniature microtome that fits inside a scanning electron microscope continues to make progress. It currently produces slices .5 microns thick; a version under development is expected to produce slices only .1 micron thick.

Other work on instrumentation involves an ultrasonic system for assessing ventricular contractility, automated measurements of turbidity in bacterial cultures *in situ,* a suction probe for surgical transection of the liver, and improved means of monitoring cerebral blood flow during and after surgery.

Analytical Methods Group

Members of the Analytical Methods Group continue to develop advanced physico-chemical methods for identifying, characterizing, and quantitating a large variety of constituents making up complex biochemical and biological systems. Recent work has included the development of techniques to fractionate complex chemical species of biologically important elements, using chromatographic methods, and then to quantify these species using electrothermal atomization and atomic absorption spectrophotometry. The Group can also apply the techniques of neutron activation analysis when it is necessary.

This work has emphasized quantitation of complex chemical species of metallic elements present in trace concentrations. Moreover, the biological samples themselves are often less than one gram. Most of the projects are conducted in collaboration with investigators in the National Institute of Dental Research (NIDR), National Institute of Mental Health (NIMH), National Institute on Alcohol Abuse and Alcoholism (NIAAA), NCI, and NHLBI.

The Group has been studying the quantitative distribution of chemical species of cis-platin, a drug used in cancer treatment. Transformations among various species occur slowly; physicians may be able to use this behavior to obtain reduced toxicity with the drug.

Collaboration with NIMH and NIAAA is continuing on the determination of very low levels (10 g/g) of vanadium in the blood and cerebrospinal fluid of normal volunteers and patients with manic-depressive behavior.

Further, in collaboration with researchers at the Oscar Lambret Cancer Treatment Center in northern France, the Group is characterizing the kinetics and uptake of trace levels of platinum complexes in cultures of human respiratory tract tumors. In some cases, where local concentrations are sufficiently high, use of a microprobe has permitted analysis of elements localized in subcellular structures. This work has been conducted in collaboration with investigators in NCI, NHLBI, NIMH, and NIAAA.

In collaboration with the NHLBI and NIMH, the Group has established a Secondary Emission Mass Spectrometer (SEMS) system used to study particle-induced ionization of biological compounds. The Group has also studied the energetics of various organic compounds in relation to the different experimental conditions that occur in organic Secondary Ion Mass Spectrometry (organic SIMS). The data reported on the energy distribution of secondary organic ions are an important contribution to the understanding of the mechanisms by which bombarding particles ionize labile compounds. In collaboration with NIMH, the Group has used SEMS to study metabolites in brain tissues that play an important role in drug-induced parkinsonism. These studies used the techniques of SIMS/MS to confirm proposed conversion of the drug MPTP into MPP in the brains of monkeys.

The Group proposes to modify the SEMS system to enable it to obtain spatial distributions of organic materials in biological specimens. This so-called "molecular microscope" will employ an ion microprobe as a primary beam and an MS/MS system for mass analysis. The computer system for controlling the microprobe and data acquisition is under development. The Group believes that imaging of organic compounds in biological specimens by this method has the potential to become a major analytical tool.

In a collaborative study with NINCDS, the Group has completed a study using analytical ultracentrifugation in an investigation of the thermodynamics of the association of the A and B chains of ricin, and extremely toxic plant protein used in the chemotherapy of leukemia. The correlation of the thermodynamics of the chemical association and toxic activity of the protein has also been studied. In addition the Group is also involved in collaborative studies with NIDR on the interactions of proteins involved in blood clotting and fibrinolysis.

Electron Beam Imaging and Microspectroscopy Group

In the past year the Group has been applying the computer-controlled analytical electron microscope and microprobe to a number of collaborative projects, as well as continuing to improve experimental and computational methods. In particular, a new cryotransfer sample stage for the analytical electron microscope (AEM) has allowed examination of frozen dehydrated and hydrated cryosections at -160 (degrees) C. This technique is important in helping to preserve elemental distributions during preparation of tissue sections.

Moreover, numerous software developments have taken place in the processing of elemental images: Electron energy-loss mapping (EELS) is now quantitative; the Group has established conditions for optimizing detection limits; and a detailed analysis has been made of the systematic and statistical errors in background fitting for the energy loss spectrum at each pixel in an image.

In collaboration with the Laboratory of Neurobiology, NINCDS, the Group is studying the distributions of potassium and calcium in rapidly frozen rat cerebella, with the aim of determining how they change following trauma. These are the first direct confirmations of movements of subcellular potassium and calcium in traumatized tissue. The collaborators are producing elemental maps of synaptosomes derived from cholinergic endings of squid optic lobe. A bimodal distribution of potassium is found in this case, indicating that only a fraction of synaptosomes are physiologically equivalent to the cholinergic endings in whole cells.

In a collaboration with the Laboratory of Oral Biology and Physiology, NIDR, the Group has made a study of mouse mandibular condyle in order to determine the role of matrix vesicles in cartilage mineralization. High calcium concentrations were found inside vesicles in the mineralization zone, but vesicles nearer the surface contained little of the element, indicating that the latter may be involved in processes other than mineralization.

In collaboration with the Pathology Branch, NHLBI, the Group has obtained EELS images and energy dispersive x-ray spectroscopy (EDS) images of lung macrophages lavaged from patients exposed to coal dust and silicates. The Group is quantifying these images to determine statistical information about the frequency and sizes of inclusions.

In collaboration with the Department of Pharmacology and Experimental Therapeutics, University of Maryland, elemental distributions are being obtained from beta cells of the rat pancreas in order to understand further the process of insulin secretion. Nitrogen images show the presence of nucleotides and proteins, while sulphur maps reveal the distribution of insulin concentrated in the secretory granules. Certain granules also contain calcium, believed to be involved in the secretion process.

Collaboration has continued with the Laboratory of Central Nervous System Studies, NINCDS, on a study of the role of elements such as calcium, aluminum, magnesium, and phosphorus in the development of amyotrophic lateral sclerosis (ALS), parkinsonian dementia, and Alzheimer's premature senile dementia. A preliminary study of the distribution of calcium in gerbil hippocampus after induced ischemia has begun with the Laboratory of Neuropathology and Neuroanatomical Sciences, NINCDS.

In both of these collaborations, quantitative elemental x-ray maps of the elements of interest have been produced using the Cameca MBX microprobe. Two major improvements in the computerization of the microprobe have increased the efficiency of the data acquisition. Additional hardware has enabled simultaneous acquisition of up to four fully background-corrected x-ray maps using an energy dispersive detector under control of acquisition software written by members of DCRT's Computer Systems Laboratory. The second improvement consists of software to focus dynamically two wave-length-dispersive spectrometers during data acquisition. Simultaneous with the EDS maps, two WDS elemental maps may now be acquired at low magnification (100x). This permits surveys of areas of up to 1mm by 1mm with no artifacts in the images due to background or spectrometer defocusing.

In other work related to image processing, members of the Group have completed work on the theory of quantitation limitations imposed by background radiation in positron emission tomography. They have now begun work on the sensitivity of fluorodeoxyglucose models to noisy data.

Nuclear Magnetic Resonance Imaging Group

Advances have taken place on several fronts—one of the most satisfying being the successful installation of commercially produced imaging equipment in the Diagnostic Radiology Department CC.

Because of the amount of steel in the floor of the NMR suite, the magnet's manufacturer could only attain a field homogeneity of 100 ppm over a 30 cm diameter, even though the specifications called for 10 ppm. By placing small quantities of steel inside the bore of the magnet in a manner calculated by the Group, it was possible to attain the specification and ensure the optimal functioning of the device.

Considerable controversy exists in the NMR imaging community over the question of whether there is an optimal field strength at which to image. By developing bench techniques for measuring signal-to-noise ratios and power absorption at various frequencies, the group is beginning to produce much-needed experimental data that will help to clarify the situation.

A collaboration with investigators at the Johns Hopkins University has produced a means of obtaining a highly selective inversion of nuclear spin populations of considerable importance in spectroscopy. This unusual result, achieved through the use of a complex hyperbolic secant puls, is only the second know analytical solution of the nonliner differential equations that govern NMR phenomenon. Moreover, above a critical threshold, population inversions appear to be independent of irradiating power.

In another development, the Group has successfully tested a novel probe design that increases signal-to-noise ratios by 40 percent, while reducing transmitter power requirements by a factor of two. The group also extended the upper frequency limit of head coil design from 84 MHz to 130 MHz with the aid of a phased-array receiving coil.

Scientific Equipment Services (SES)

SES is continually updating equipment and services provided to keep abreast of changing technology. For example, a second numerically-controlled milling machine has been purchased which will permit rapid fabrication of unusually shaped molds used by BEIB's Plastics Unit.

The Scientific Equipment Rental Program (SERP) has expanded the variety of instruments it provides, such as microcomputers that can control other laboratory instruments. SERP has also instituted procedures that will permit researchers to exchange instruments that are no longer needed for credit against future rentals.

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The automated catalog in the NIH Library not only identifies items in the collection but also tells users whether any particular item has been checked out.

Library Branch

Carolyn Brown, Chief

The NIH Library has spent much time this year analyzing operations to gain efficiency. The emphasis is on better service at the same or a lower cost. A space study completed early in the fiscal year pointed out the shortage of reader space in the NIH Library compared to other medical libraries of relatively similar size and purpose. As a result of this study, the Library has requested more space and has been given assurance that the patio outside the reading room will be enclosed, and that further expansion is also possible. Every effort has been made to make effective use of the available space.

The DRS Management Analysis Office performed a study of after-hours usage of the Library to determine the make-up of clientele during evening and weekend hours. A survey of actual users and of the shelving and circulation workload was conducted for 29 days in May and 28 days in November 1983. The period surveyed was the time between 5:30 p.m. and midnight on weekdays and the entire weekend hours.

The major findings of this survey were:

- An average of 73 patrons per day visit the Library during the evening hours from 5:30 p.m. to midnight. These include NIH patrons (principally fellows and associates) and non-NIH patrons (principally students).
- Between 10:00 p.m. and midnight an average of 30 patrons use the Library facilities; 10 are NIH staff.
- Seventy-three percent of the evening NIH patrons indicated no hardship would result if the Library closed earlier.

As a result of these findings, the Library Advisory Committee and the Scientific Directors approved a change of weekday closing hours from 12 midnight to 10:00 p.m. The change allows redeployment of personnel to peak hours, which should provide better service. Savings in cost for utilities, maintenance, and depreciation of materials also result.

A study of the management of photocopy requests, carried out over a number of weeks, has led to a complete reorganization of the work flow. Photocopy requests are now being handled with a 24-hour turn-around in cases where no problem is encountered.

The DRS Management Analysis Office provided guidance in several studies made in anticipation of evaluating the online catalog. An intensive analysis was made of the use of the card catalog and other manual files by Library clientele. The results will provide baseline data to compare with a future study of the online catalog. The issues covered are: type and success rate of researches in the catalog; average number of users at the catalog at one time; average time required to locate an entry in the catalog; and effect of experience on the success rate.

The Technical Services Section also made a detailed collection of statistics on work performed in the process of cataloging a new book, with times measured for each step. The resulting figures will aid in evaluation of improvements made with the new online catalog. This is also the first step in developing item costs, and in ensuring the most effective use of time and staff.

The Library staff has inauguarated a series of lectures on current topics in bioscience featuring prominent speakers from NIH research programs. With five lectures a year, the series provides one means for keeping staff informed on developments at NIH and the biosciences in general.

Improvement in Service

Improved service has been the result of attempts to streamline operations. One example is the reorganization of photocopy operations, already mentioned above, which has produced a speed-up in the processing of photocopy requests. The number of requests received for photocopying from library materials has increased approximately 24% from 1983 to 1984, from 14,500 to 19,000 articles.

The number of interlibrary loans processed increased approximately 13%, from 8,700 to 10,000 requests.

Assistance to NIH authors in verifying bibliographies before publications has increased. At least one staff member was assigned monthly to correct bibliographies numbering 35 to 130 citations. This service is expected to generate further demand as NIH researchers become aware of it.

A cooperative effort between the Division of Computer Science and Technology and the Library provides NIH scientists with monthly citations from *Biological Abstracts* on a floppy disc compatible with the IBM Personal Computer and the Apple microcomputer. The Library develops the profile while DCRT gives advice on the software package required to manipulate the output. The service also allows for monthly output in printed form.

The Library published the fourth edition of *Current and Noncurrent Journals: NIH Library*, a much needed update on the edition published six years ago. This volume, which is distributed to NIH personnel upon request and to selected outside libraries and organizations, allows determination of most facts about the journal holdings without a trip to the Library.

The amount of money spent on contract translations decreased greatly in fiscal 1984 from that spent in 1983. With the addition of one translator who commands several additional languages, most requests can be handled inhouse to the complete satisfaction of the client.

Automation

Much time of the Library staff was spent in correcting the bibliographic file in preparation for automation. Toward the end of the year a contractor group came in to accomplish the time-consuming task of barcoding every item in the collection and entering the barcode number into the automated file record for that item. Because of difficulties of using an incomplete file, the online catalog was not offered for public use until after the end of the fiscal year.

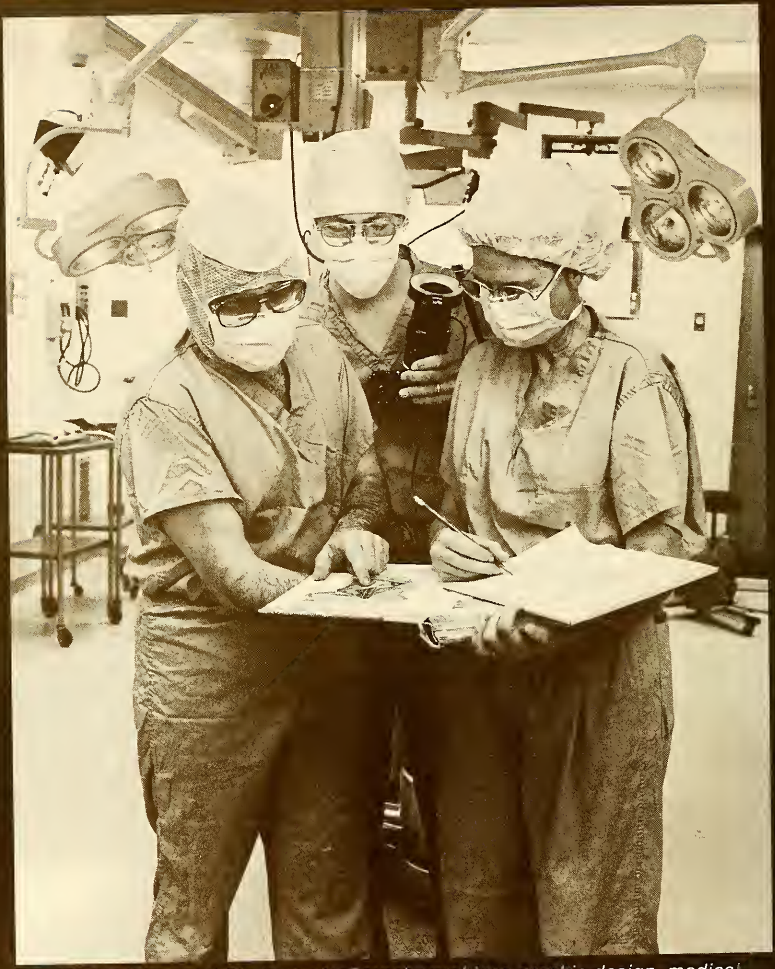
Reorganization

In the course of automating, observation of work relationships and work patterns led to recommendations of organizational changes. In a Library-wide reorganization effective in July, five members of the Circulation Unit moved into the Reference and Bibliographic Services Section. Circulation will work more closely with the reference staff in particular as automation progresses. Two circulation staff members transferred to the Interlibrary Loan Unit, which takes over processing of requests for photocopy of library materials. The Technical Services Section was split into three units instead of the former two, and is now organized by function. A Cataloging Unit, Acquisitions Unit, and Bindery Unit replace the previous Monographs Processing and Journals Processing Units.

Services of the NIH Library

The NIH Library offers a full array of services to assist scientific investigators in their work. They include:

- **Computer Bibliographic Searches** - Specialists perform computerized literature searches and compile bibliographies upon request. The staff is experienced in retrieving citations and abstracts from some 155 scientific databases. (Request from Reference and Bibliographic Services.)
- **Current Awareness Service** - The Library's Selective Dissemination of Information (SDI) program provides users with regular computer updates on new literature in the biological and medical sciences. (Request from Reference and Bibliographic Services.)
- **Reference Services** - Reference librarians not only answer reference questions on site or by telephone (496-2184), but also advise users of other library services that may meet their needs.
- **Photocopying** - Photocopying machines are available to users. (Photocopy Service, lower level.) The Library also fulfills copying requests. (Request form at Circulation Desk.)
- **Microfilm and Microfiche** - Many journals are also kept in microform. Most are backfiles of important titles, acquired in order to save space. Reader-printers are located nearby.
- **Circulation** - Books other than reference works and non-circulating reserve items can be checked out. Second copies of some of the most popular journals are also available for circulation.
- **Interlibrary Loans** - Research publications not in the collection can be obtained from other libraries. Photocopies of journal articles obtained from the National Library of Medicine are usually provided in one to three workdays.
- **Translations** - Foreign language scientific materials are translated at request, and the translations are made available to other users as well.
- **Stacks Service** - Library staff will search for any volume a user cannot find on the shelves.
- **Monthly Acquisitions List** - This list, "Recent Additions to the NIH Library," is available in printed form and on the NIH Wylbur computer system.
- **Library Tours** - A tour with explanations of NIH Library services and policies is available every Wednesday at 2 p.m., beginning from the Reference Assistance Desk.
- **Carrels** - Private study carrels are available on a limited, first-come basis. (Circulation Unit.)



The Medical Arts and Photography Branch combines graphic design, medical illustration and photography in the service of clinical research.

Medical Arts and Photography Branch

Ronald B. Winterrowd, Chief

The Medical Arts and Photography Branch (MAPB) provides multi-media visual communication services to the NIH community, documenting medical research programs, accomplishments, and scientific data through photographs and graphic illustratons for publication and for presentation at conferences. MAPB provides numerous services to meet all information needs.

The Branch's staff of professional artists, photographers, and other specialists have extensive expertise in converting data into effective presentations. They are highly skilled in meeting the needs of scientists for graphic presentation, medical arts, and still and motion picture photography, including photomacrography and photomicrography. Services included design and production of publications; preparation of slides, vugraphs, and other projected visual aids; animation artwork; exhibit design; statistical drafting; display charts; posters; and medical illustrations and three-dimensional models.

The philosophy of the Branch is to provide high quality professional services competitive in cost with commercially obtainable services. On contracted work, the staff works closely with vendors of design, graphic and photographic services to ensure that MAPB's quality standards are maintained.

This year, MAPB established an advisory committee of seven intramural scientists and information specialists to represent its users: informing the Branch about users' concerns and expectations and informing the users about MAPB services. The committee reviews the services and recommends improvements, new services, and discontinuations. It also shares in evaluating alternative methods of producing graphics products, presents options to the users, and tells MAPB what the users prefer.

The Branch continued sending a team of staff members to NIH laboratories and other units to explain its services, inform users of cost-saving measures, and obtain suggestions on how services can be improved. Units in every Bureau, Institute, and Division have been visited, and MAPB wishes to remind its users that staff will gladly visit any NIH unit, no matter how small, for an information exchange.

Although procurement regulations require negotiations only for bids over $500.00, MAPB continued to hold bid sessions for all graphics work performed by outside vendors in order to obtain the lowest possible cost for the user.

Photography Section

The Photography Section's requests for services increased by 6.1 percent during the year. Photography support services in photomicrography, photomacrography, clinical photography, information photography, and photographic technical information, as well as photographic laboratory services, were provided to NIH investigators by highly trained technicians using advanced equipment.

The Section moved into newly renovated space in the Clinical Center, in the same area as the Branch office and the other sections of MAPB. This move allows for improved total services to NIH investigators. A new Zeiss ICM 405 inverted microscope for performing photomicroscopy with transmitted light and for time-lapse video recording was added to the Photomicrophy Unit. Time-lapse video offers possibilities such as viewing cell development, growth of bacteria, and even cell division; it also eliminates delay for film development.

To supplement in-house laboratory services, the Section continued to obtain the services of private photographic facilities in the Washington, D.C. area.

Motion Picture Section

The Motion Picture Section increased utilization of existing equipment and facilities, and also acquired selected new equipment. As a result, sophisticated film production will be possible at a lower cost to our users, and the use of new raw stock materials will provide better quality and substantial energy savings. In addition, the Section began producing high quality transparencies and film strip masters. The expanded services benefit users by reducing costs and time required.

Design Graphics Section

This Section is composed of professionally trained, highly skilled and experienced designers and illustrators. Many have won awards in local, national, and international art competitions. The Section provides the NIH scientific community with graphic and design art for scientific presentations and in public information; this includes illustrations, publications, posters, exhibits, and slides, as well as the design and preparation of support materials for various conferences organized at the NIH.

Both the Design Unit and the Graphics Unit experienced an increased demand for services this year, resulting in a 19 percent increase in total production units over FY 1983. Section Staff coordinated 97 percent of Graphics Unit and 88 percent of Design Unit job requests with local private companies. These companies participate in competition and bid sessions with other vendors; this process ensures the lowest possible price to the user. The Section continues it efforts to keep costs down, while maintaining the quality of artwork and high productivity levels.

During the past year the Graphics Unit enlarged its computer graphics capacity by adding a computer-generated color slide system. The system stores the information for the requestor on a floppy disk, which eliminates the need to store board art; if a change is needed later, the disk can be revised. It also produces black and white slides from which prints can be made for publications.

Medical Illustration Section

This section is staffed with talented, highly trained artists who possess a broad background in medical science. Their workload remained constant. Job requests included medical models; surgical illustrations for scientific papers, books, and slides; and similar projects.

More than 200 anatomic drawings were completed for the *Atlas of Extremity Sarcoma Surgery.* The book's 15 chapters have also been published as separate articles in the surgical literature.

Three 3-dimensional heart models were fabricated for the National Heart, Lung, and Blood Institute; they demonstrate (a) heart valve replacements, (b) four anastomotic positions in arterial bypass surgery, and (c) the "Morrow operation" for correcting idiopathic hypertrophic subaortic stenosis.

Outlook for FY 1985

MAPB is planning an internal reorganization early in FY 1985 that will allow the coordination of diverse artistic talents, services, and goals of the Branch into a more efficient and effective organization to serve the NIH community.

The Branch also plans to issue a brochure explaining its services and informing users of ways to cut their own expenses for MAPB services and products.

Branch-wide efforts at cost containment will continue. The Design and Graphics Unit will reduce in-house hourly rates in FY 1985. The surcharge for all contract work will remain at 10 percent.

The Embryo Cryopreservation Program of the Veterinary Resources Branch freezes and stores laboratory rodent embryos to help ensure the survival and genetic purity of valuable strains.

Veterinary Resources Branch

Robert A. Whitney, Jr., D.V.M., Chief

The Veterinary Resources Branch (VRB) provides professional and technical support services for NIH intramural programs. It is responsible for

- Production of defined research animals
- Procurement, quarantine, conditioning, and issuance of animals from outside sources
- Management of a central animal surgery and radiology facility
- Animal disease diagnosis and control
- Research holding for primates, cats, dogs, rodents and livestock
- Consultative services on animal health, care, husbandry, genetics, and nutrition
- Maintenance of an international laboratory animal Genetic Resource
- Administrative support of the Interagency Research Animal Committee.

During FY 1984 the Branch continued to be active in meeting all of these responsibilities.

The declines in animal use by the Institutes over the past three years appeared to lessen in 1984, and current trends suggested that the situation may be stabilizing. VRB efforts continued to be directed towards reducing the cost of services and increasing efficiency of operation. Staff has been reduced in programs where demand has markedly declined, and an evaluation was initiated, with participation from the NIH Division of Management Policy, to better define personnel and space requirements for certain animal production and related activities. In addition, contract services were sought for an in-depth assessment of VRB programs to identify those which should be further modified or expanded to better meet projected needs, and those which may not be of vital importance to NIH. Several contracts were modified or eliminated to reduce costs, as well. Authorization was obtained to sell animals declared excess to NIH needs to other Government agencies and to NIH grantees. This provided income to support specialized animal production colonies during fluctuations in NIH intramural requirements.

VRB continued to provide administrative support for the Interagency Research Animal Committee (IRAC) and the NIH Animal Research Committee (NIHARC). IRAC was active in developing and reviewing and providing advice on documents such as the "U.S. Government Principles for Biomedical Research involving Vertebrate Animals Used in Testing, Research and Training" and the Council of International Organizations of Medical Sciences' "Principles for The Protection of Laboratory Animals." Contracts with The World Health Organization and the Pan American Health Organization (PAHO) were continued to assist participating countries to develop national primate programs. Because of the almost total unavailability of commercial primate supplies from South America, requests for animals through the PAHO contract were more than twice the number received in any previous year. The NIHARC completed the Manual Chapter "Care and Use of Laboratory Animals in the Intramural Program," which establishes responsibilities of the Institutes' Animal Research Committees. For the first time in over a decade, a census of research animals maintained by NIH was conducted; more than 360,000 animals, occupying over 360,000 square feet of space, were counted.

Animal Center Section

The NIH Animal Center in Poolesville, Maryland, acquires, produces, maintains, and develops large research laboratory animal models and provides related services and products for NIH investigators. The animals involved are mainly primates, farm animals, dogs, and cats. Requirements for defined foxhounds, beagle, pointers, miniature swine, and several species of monkeys are provided by breeding colonies.

The number of nonhuman primates purchased, quarantined, conditioned, and issued remains low; but research holding of monkeys for NIH institutes continued at a high level. Services and facilities were also provided under interagency agreements for studies on monkeys belonging to the Food and Drug Administration (FDA) and the Department of Defense (DoD). Contract costs for the production of rhesus monkeys at Perrine, Florida, were reduced, and an assessment of NIH continued needs for animals from this source was initiated.

A slight reduction in the total population of livestock was coupled with a significant increase in the number of blood collection procedures performed and quantities of blood issued. Increased blood issues were largely in support of artificial heart valve surgery conducted by the National Heart, Lung, and Blood Institute (NHLBI)

Inbreeding of miniature swine was continued for the National Cancer Institute (NCI) in support of its research in transplantation immunology; the eleventh generation of inbreeding was achieved in one of the lines. Excess animals were made available to the US Department of Agriculture (USDA) and other institutions. Swine were also being held for long-term atherosclerosis studies by the NHLBI.

Production of foxhounds was below the projected number because of neonatal mortality and parvoviral infections. The Institutes' requirements were met by providing foxhound type dogs purchased from the DoD. Production of normal and "anxious" pointers for the National Institute of Mental Health (NIMH) progressed satisfactorily, and Animal Center facilities and services were provided for studying them. The number of beagles raised for NCI toxicology programs continued to increased (Figure 1); dogs not used for those purposes were made available for other NIH research programs.

The inbreeding of foxhounds was discontinued because of the results of a survey which showed insufficient interest of investigators in using inbred dogs. Maintenance of a breeding colony of moustached tamarians *(Saguinus mystax)* for the FDA was discontinued because of poor reproductive performance

A variety of collaborative research activites were actively pursued. Those involving nonhuman primates were in the fields of endocrinology, behavior, psychology, nutrition, reproduction, athersclerosis, and husbandry. They were undertaken with investigators from the National Institute of Child Health and Human Development (NICHD) National Institute of Allergy and Infectious Diseases (NIAID), NIMH, NHLBI, and VRB. Reproduction was the principal field of study in livestock and involved artifical insemination, embryo transfer, and the investigation of spontaneous cystic endometrial hyperplasia; participating institutions were the NCI, Smithsonian Institution, and Clemson University. Endocrinology and reproduction were also a focus of attention for collaborative studies in dogs with investigators at the Uniformed Services University of the Health Sciences (USUHS) and the Smithsonian Institution.

Small Animal Section

The Small Animal Section (SAS) provides rodents and rabbits from its production colonies and also manages contracts for this purpose. It manages the NIH Animal Genetic Resource, which contains more than 250 defined strains and stocks and has programs devoted to animal model development, nutrition, health, embryo cryopreservation, and research rodent holding.

Figure 1
Issues of Research Dogs

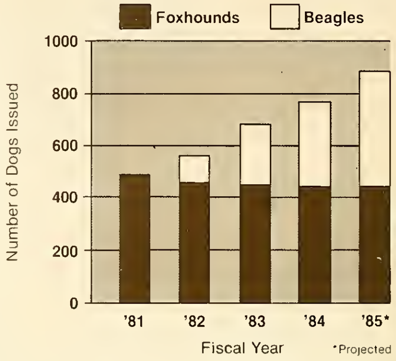
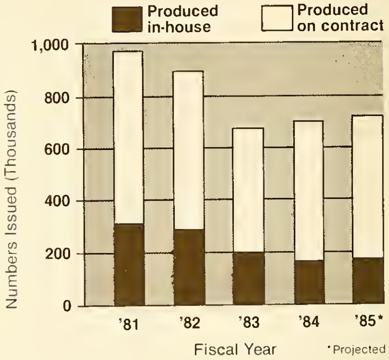


Figure 2
Rodents and Rabbits Issued



The SAS issued approximately 700,000 animals (164,000 from in-house and 536,000 from contract sources) which represented an increase of 5 percent compared to 1983 (Figure 2). Rodent holding and research support activities initiated in 1983 were heavily used. Despite several delays related to renovations, the facility achieved an occupancy rate of approximately 80 percent. Approximately 30 investigators representing 8 institutes used this service in 1984.

Several adjustments were made in the production colonies in response to changes in BID requirements. Inbred guinea pig production was reduced approximately 40 percent and rabbit production was increased by 30 percent. Watanabe rabbits were introduced into the production colony at the request of the NHLBI as the initial step in establishing a breeding colony. This strain has a naturally occurring hypercholesterolimia that is useful in studying atherosclerosis; the demand for it is expected to exceed supply for several years because the survivability of offspring is poor.

A new autoclave was installed in Building 14G, allowing barrier activities to return to normal. Thirty-eight stocks and strains of mice were hysterectomy-derived and reintroduced into this facility to replace those contaminated with mouse hepatitis virus in 1982. Alseth and OH guinea pigs were added at the request of the NIAID, where they will be used for immunologic studies.

No new commercial contracts were awarded for small animal production. A contract for inbred guinea pigs was terminated because of the decrease intramural demands for them. Several production contracts for small animals were consolidated into a single contract to increase efficiency in their administration. Functional requirements for the automated animal data management system was finalized; the external designs for the small animal breeding, ordering, and inventory were completed; and certain hardware (minicomputer and accessories) was purchased.

The embryo cryopreservation program experienced a very successful year. Eight stocks and strains were frozen and stored for future use. Superovulation trials, which are necessary to determine maximum ova production, were completed for 14 strains. Several new preservation techniques were evaluated and yielded valuable information.

The animal health program was expanded to include veterinary support for the research holding activities. A major outbreak of cecitis in the rabbit colony was associated with high mortality among weaned animals and young adults and resulted in a brief shortage of rabbits for issue to the Institutes.

Mortality in the guinea pig colony decreased slightly following the correction of nutritional problems, but it is still unacceptably high; investigation to ascertain the cause is continuing.

Expansion of research holding activities resulted in an increased demand for nutrition-related services. Several investigators required special diets for their studies. Collaborative studies with investigators in the National Eye Institute (NEI) and NHLBI continued this year. A new, gluten-free diet for callitrichids was developed and tested in several colonies; its use was associated with marked improvement in the physical condition of the animals.

Comparative Pathology Section

The Comparative Pathology Section (CPS) characterizes the health status of laboratory animals produced or used at the NIH. It studies their naturally occurring diseases and develops procedures to control or prevent them. The Section also maintains a program to ensure the genetic definition of rodents produced by VRB for intramural programs and supplied to other institutions for use as breeders. The Animal Disease Investigation Service (ADIS) managed by this Section provides diagnostic services for intramural investigators as well as consultation and advice concerning the management of animal colonies.

The number of necropsies performed by the Pathology Unit decreased by 13 percent as a result of lowered deaths from correcting nutritional problems in the guinea pig colonies. Numerous necropsies were performed for investigators, in conjunction with ADIS, to assist them in distinguishing naturally occurring from experimentally induced conditions in laboratory animals.

The number of samples from in-house and contract sources of animals that were examined by the Microbiology Unit for parasites and evidence of viral infection was 4 percent more than last year. This increase was due to increased serologic testing of mice in the barrier area to evaluate the borderline positive test results for mouse hepatitis (MHV). Extensive testing failed to demonstrate MHV infections. Most of the borderline positive of results occurred in mice with NAB background, indicating that the low level positivity may have been due to the presence of autoimmune antibodies. Hepatic lesions in some of the mice also may have been the result of autoimmune disease. None of the sentinel nude mice, which are highly susceptible, had lesions of mouse hapatitis. As a result of knowledge gained concerning the propagation of Tyzzer's bacillus (Bacillus piliformis) within the host cell, it was possible to produce a concentrated, clean antigen for use in developing a Tyzzer's disease enzyme-linked immunosorbent assay (ELISA). This assay will be helpful in epidemiology studies and in learning more about the natural history of this intriguing disease. Similarly, the recent isolation of a cilia-associated respiratory (CAR) bacillus of the rat in embryonated hen's eggs provided a means of preparing a concentrated, clean antigen, and the development of a specific ELISA. Its wide use is anticipated in studies to elucidate the etiology of chronic respiratory disease of rats and to investigate the role of this agent in diseases of other animals.

The Animal Disease Investigation Service (ADIS) responded to requests for assistance from the Institutes at a level 9 percent higher than last year (Figure 3). One cause of the increase was the conversion of Building 14B to a research holding facility. When an animal belonging to an NIH researcher dies in this facility, the pathology examination is listed as an ADIS response.

The number of permits for introduction of rodents and rodent products declined by 27 percent. The number of permits issued tends to be quite variable from year to year according to the activities of the Institutes, and it is difficult to predict.

Approximately 200 rats and 900 mice from the Genetic Resource were monitored by the Genetics Unit. No genetic contaminations were reported or detected in any of the Genetic Resource colonies. Rederivation of the mouse foundation colonies due to mouse hepatitis virus and the physical reorganization of the SAS rodent colonies resulted in relatively low numbers of animals being submitted for monitoring early in the year. Based on current trends, however, it is anticipated that the routine monitoring workload will be approximately 1300 animals.

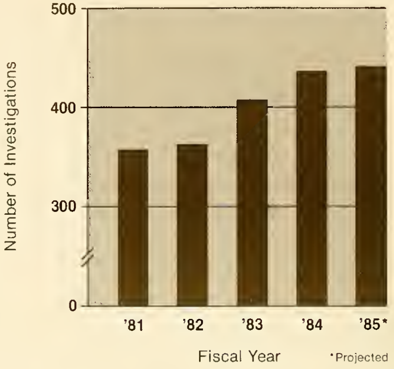
Routine monitoring was significantly expanded during the year; genetic profiles for two new inbred mouse strains, ICR and CfC3t, were established, and congenic lines of rats (7) and mice (5) were added to the monitoring program. Routine testing of F1 hybrids from the production colony was initiated and represents the first in a series of steps to examine the genetic quality of animals bred for general use. Monitoring of the F1 breeding colonies will result in the need to test about 250 additional mice per year. A number of genetic investigations were conducted with respect to several mutations that occurred in VRB colonies and elsewhere. The number of outside requests for assistance under the Genetic Investigation Service was 25.

Veterinary Medicine and Surgery Section

The Veterinary Medicine and Surgery Section has centralized facilities for research animal holding and experimental surgery. It provides comprehensive veterinary medical service, animal care, and consultation in developing animal models for intramural research protocols.

The Surgery Unit handled approximately 1000 cases, which represents a slight increase over the last year in both number and complexity of procedures being performed. In addition to equipment required for routine surgical monitoring, new devices were provided to measure cardiac output and blood flow. A technique was developed to permit chronic collection of cerebrospinal fluid from sheep, pigs, and nonhuman primates using catheters implanted in the fourth ventricle of the brain. This technique permits investigators to study cerebrospinal fluid physiology and to test chemotherapeutic agents of potential use in treating tumors of the central nervous system.

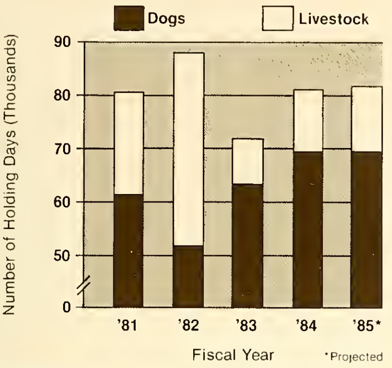
Figure 3
Animal Disease Investigations



The Comparative Medicine Unit maintains centralized holding space on the Bethesda campus for large laboratory animals. Almost all of the available space was utilized, and no major changes in requirements are anticipated. The majority was used to house dogs and sheep for cardiovascular research projects and for dogs and swine used in a variety of projects related to cancer therapy (Figure 4). Professional and technical support was provided for studies involving small groups of dogs and cats which were used by the NIMH as models for Parkinson's Disease. The use of piglets for the development of a vaccine against rotavirus continued, and a long-term commitment was made to house chickens for use in avian malaria research.

The Primate Research Unit increased its research holding to nearly 1100 nonhuman primates. The demand for holding services is expected to decline in FY 1985 because of the abolition of NICHD's Pregnancy Research Branch, but other institutes have projected increased requirements which will result in a need to maintain 900 animals. Nonhuman primates continued to be available through the recycle program, which permits investigators to obtain nonhuman primates at substantial cost savings while conserving this animal resource. The timed-pregnant breeding colony was phased out, but the unit will continue to provide professional and technical services as requested to produce timed-pregnancies using investigator-owned monkeys.

Figure 4
Large Research Animal Holding — Bethesda



The unit provided continuing postoperative care for nonhuman primates in support of NHLBI research, assisted NIAID in its malaria research, and made services available to NICHD in its pregnancy and perinatal studies.

Outlook for 1985

It is anticipated that provision of animals and related services will be near the levels of 1984 if procedures for cost accounting and rate setting remain as they have been in the past. However, VRB costs would be profoundly affected by proposed changes in NIH fiscal accountability procedures. Implementing full cost recovery, including existing Management Fund costs, would significantly increase costs of animals and VRB services. Recommendations for modifications of programs and user needs will be implemented to improve VRB's responsiveness to NIH needs and effect cost reductions.

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